Heterogeneity of Clinical Manifestation of Hypertrophic Cardiomyopathy Caused by Deletion of Lysine 183 in Cardiac Troponin I Gene

Insight From Two Autopsy Cases With an Identical Sarcomeric Gene Mutation

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Summary

Hypertrophic cardiomyopathy (HCM) is associated with gene mutations that encode sarcomeric proteins. However, the relationship between genotype and histopathologic findings is unclear. We report on two autopsy cases with advanced HCM associated with deletion of lysine 183 mutation in the cardiac troponin I gene. One case, a 74-year-old female exhibited dilated cardiomyopathy-like features. Transmural scarring was diffuse and circumferential, involving the whole left ventricle, especially the ventricular septum which was replaced with extensive fibrosis and showed marked wall thinning. The other case, a 92-year-old male revealed typical HCM findings. Patchy scars which corresponded to replacement fibrosis were found extending from the septum to the anterior wall. These two autopsy cases indicate the clinical heterogeneity of HCM even within the same disease-causing mutation and suggest that the degree and extent of fibrosis determine differences in the clinical manifestations of HCM. This is the first autopsy report that demonstrates identical sarcomeric gene mutations causing different clinical manifestations and histologic findings. The findings suggest that additional genetic or environmental factors influence the phenotypic expressions and clinical courses of HCM caused by genetic mutation of sarcomeric proteins. (Int Heart J 2010; 51: 214-217)

Key words: Dilated phase of hypertrophic cardiomyopathy, Histology, Fibrosis

Case Report

Case 1: This female patient was 74 years-old at the time of death. She had experienced chest pain on exertion from 50 years of age. At 52, an echocardiogram showed marked asymmetric septal hypertrophy (ASH) with systolic anterior motion (SAM) of the anterior mitral leaflet. The interventricular septum (IVS) to the left ventricular (LV) posterior wall (PW) ratio was 20 mm/8 mm, LV end-diastolic dimension (LVDd) was 46 mm, and her ejection fraction (EF) was 62%. At this time, she was diagnosed with HCM. Her genetic analysis revealed a Lys183del mutation in the cTnI gene. Examination of her familial genetics demonstrated that some family members had HCM associated with the same mutation. At 55, a pacemaker was implanted for bradycardia due to atrial fibrillation (AF). At age 57, in spite of medical treatment with digoxin and diuretics, the signs and symptoms of congestive heart failure became progressively worse and electrocardiography began to show gradual changes in systolic dysfunction. The IVS to PW ratio changed to 18 mm/8 mm, and the LVDd was 51 mm and EF was 39%. Therefore, she was thought to have devel-

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Received for publication October 5, 2009. Revised and accepted February 8, 2010.
oped end-stage HCM from typical HCM. The medications pimobendan and carvedilol were added to her treatment regimen. At 73 years of age, she had typical DCM-like features. Echocardiograms revealed LV dilatation (LVDd = 61 mm), systolic dysfunction (EF = 29%), no ASH (IVS to PW ratio = 8 mm/8 mm), and no SAM (Figure 1). She died of cerebral infarction in spite of medication with warfarin for AF. At autopsy, her heart weighed 410 g, and macroscopically there was severe dilatation of the right and left ventricular cavities. Transmural scarring was diffuse and circumferential, involving the whole LV, especially the ventricular septum and the contiguous anterior wall. Histologically, the septal wall was replaced by extensive fibrotic tissue and showed marked thinning. Bizarre myocardial hypertrophy and disarray were also found. No stenotic lesions were observed in the epicardial coronary arteries (Figure 2).

Case 2: This male patient died at the age of 92 years. At age 80, he was diagnosed with angina pectoris and was treated with daily oral doses of aspirin and nitroglycerin. At 85, he experienced dyspnea on exertion and was diagnosed with HCM with diastolic heart failure. The IVS to PW ratio was 14 mm/10 mm, LVDd was 41 mm, and EF was 67%. At this time, he was treated with diuretics for diastolic heart failure. A mutation identical to that of case 1 (Lys183del in cTnI) was identified. His familial genetics demonstrated that some members of the family also had HCM associated with the same mutation. At age 90, echocardiograms still showed typical HCM findings. The IVS to PW ratio was 17 mm/9 mm, LVDd was 44 mm, and EF was 60%. He died of heart failure due to acute myocardial infarction in the postero-lateral wall. At autopsy, his heart weighed 450 g, and macroscopically there was severe dilatation of both the left and right ventricles. Severe narrowing and transmural scarring of the septum was found. Scale = 0.1 cm. (B) Massive fibrosis was observed in the entire left ventricular wall, especially in the septum, and was particularly notable in the middle and epicardial regions of the LV; the subendocardial region was less involved (Mallory-Azan stain). (C) Myocyte disarray in the lateral wall (hematoxylin and eosin stain, × 100). (D) Massive fibrosis in the interventricular septum (Mallory-Azan stain, × 100).
**DISCUSSION**

HCM caused by cTnI mutations is rare. Indeed, cTnI mutation was associated with less than 6% of HCM in most large series studied to date.\(^5\,6\) Lys183del in the cTnI gene was first reported to be one of the mutations that cause HCM in 1997.\(^7\) We previously reported that HCM caused by the Lys183del in the cTnI gene has a high penetrance in subjects > 20 years old and is associated with sudden death at any age. Furthermore, about 30% of patients with HCM caused by Lys183del developed systolic dysfunction accompanied by a decrease in septal wall thickness after 40 years of age. Moreover, 19% of patients with HCM caused by Lys183del displayed DCM-like features. LV wall thinning and systolic dysfunction were generally found in about 10 to 15% of referral-based HCM patients.\(^7\,8\) Therefore, HCM caused by Lys183del leads to systolic dysfunction more frequently than those caused by other gene mutations.

In the end-stage of HCM, which is defined as EF < 50%, some patients demonstrate LV wall thinning or LV dilatation, although others show persistent hypertrophy with nondilated LV.\(^9\) Evolution from typical HCM to the end-stage of HCM is related to the progression of fibrosis.\(^9\,10\) The fibrosis in the LV wall is usually extensive in the septum,\(^11\) however, Yutani, et al reported that the fibrosis is most extensive in the lateral wall.\(^10\) Therefore, the degree and extent of fibrosis in HCM is varied. Disarray might be a predisposing factor for fibrosis because of widespread disarray contacting with fibrosis.\(^12\) Small vessel disease has also been postulated to be a cause of fibrosis.\(^13\) On the other hand, Varnava, et al reported that fibrosis and small vessel disease are unrelated to disarray.\(^14\) Therefore, the mechanism of fibrosis is uncertain, and the reason for progression of fibrosis that determines the prognosis of HCM has not been clarified to date. In our cases, a significant degree of fibrosis was observed in the middle and epicardial region of LV and the subendocardial region was less involved as compared to that of disarray. Case 1 showed a more severe fibrosis compared with case 2, particularly in the septal wall. From these two autopsy cases of HCM caused by Lys183del with different clinical manifestations, we infer that the degree and extent of fibrosis are closely associated with the differences in the clinical manifestation of HCM.

We have presented the two HCM cases caused by Lys183del in cTnI gene exhibiting different clinical manifestations; one was a typical HCM and the other showed typical DCM-like features. We previously reported that siblings with HCM caused by the Arg92Trp mutation in the cardiac troponin T gene showed the same autopsy findings of DCM-like features.\(^15\,16\) and some members of their families showed typical HCM findings by echocardiography. Therefore, there may be additional genetic or environmental factors because these differences could not be explained only by disease-causing gene mutations. From the literature, the candidate genetic or environmental factors that can result in these pathologic differences have been reported to be as follows: (genetic modifiers) the insertion/deletion of angiotensin-converting enzyme, angiotensin II type I receptor A/C1166 polymorphisms; (environmental factors) ischemia, hemodynamic alterations, neuro-hormonal activation, oxidative stress, and cytokines.\(^7\,10\) In addition, although the predisposing or precipitating causes of end-stage HCM are not fully clear at this time, it is reported that end-stage patients are diagnosed at an earlier age and have more severe symptoms at initial evaluation than non-end-stage HCM.\(^9\) Age at diagnosis and onset of HCM symptoms were earlier in case 1 than in case 2. These differences may have influenced the clinical manifestations.

In conclusion, two subjects with HCM caused by an identical Lys183del mutation in their respective cTnI genes showed different histopathologic findings and clinical manifestations. These observations seem to be useful to understand the heterogeneity of HCM and suggest that other modifying factors influence phenotypic expressions and the clinical courses of genotyped HCM. Further evaluations of HCM with an identical underlying sarcomere-related gene mutation based on genetic analysis might provide valuable information and may contribute to risk stratification.

**REFERENCES**